PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference R 43875	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/007540	International filing date *(day/month/year)* 09.07.2004	Priority date *(day/month/year)* 11.07.2003
International Patent Classification (IPC) or national classification and IPC A61K39/29, C07K14/18		
Applicant INTERCELL AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.01.2005	21.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Brouns, G Telephone No. +31 70 340-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/007540

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-50 as originally filed

   Claims, Numbers

   1-33 as originally filed

   Drawings, Sheets

   1/1 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☒ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	-
	No:	Claims	1-3, 5, 11-14, 16-26, 31-33
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-3, 5, 11-14, 16-26, 31-33
Industrial applicability (IA)	Yes:	Claims	1-3, 5, 11-14, 16-26, 31-33
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

The present application relates to hepatitis C virus (HCV) vaccines, comprising multiple T cell epitopes. Some combinations have been tested in a mouse model and on healthy human volunteers.

1) Reference is made to the following documents:

D1: WO 01/21189 A1 (EPIMMUNE INC; SETTE, ALESSANDRO; SIDNEY, JOHN; SOUTHWOOD, SCOTT; LIVIN) 29 March 2001 (2001-03-29)
D2: US-A-5 683 864 (HOUGHTON ET AL) 4 November 1997 (1997-11-04)

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

ARTICLE 5 AND 6 PCT

2) The present application relates to HCV vaccine compositions comprising at least two and up to twelve different HCV epitopes, selected from 23 different 'hotspot epitopes'. A hotspot epitope is defined in the application as 'a short peptide comprising two or more epitopes shortly after each other, directly after each other or partially or fully overlapping'. Such hotspot epitopes are known in the art, for instance D1 discloses the binding capacity of peptide AAYAAQGYKVLVLNPSVAAT to different HLA-DR molecules (D1, table XXXIV). Furthermore, the claims are not related to said hotspot epitopes per se, but to **epitopes derived from a hotspot epitope**. HCV epitopes are well known in the art, in particular D1 lists a large number of HCV peptides that are known to bind to various HLA alleles, and the epitopes identified in D1 (claim 1; tables XXVI and XXXII) may be found in the hotspot epitopes of the present application.
D1 relates to HCV vaccine compositions comprising between 1 and 8 HCV peptide epitopes, therefore each of the combinations of 2-8 HCV epitopes claimed in the present application relates to a separate solution of providing further HCV vaccines. This results in over 145.000 inventions, if only full length hotspot epitopes are considered, and a multitude of said number if every possible epitope within each hotspot epitope is taken into consideration.

Only a very small number of said combinations is considered to be disclosed and supported in the sense of Articles 5 and 6 PCT, namely the compositions used to induce an immune response in the HLA-A2 transgenic mouse (peptides 83, 84, 87, 89 and 1426, example IV) and in the pilot study in healthy human individuals (peptides 84, 89, 1426, example VII).

Examination with regard to novelty, inventive step and industrial applicability is restricted to subject-matter that fulfils the requirements of Articles 5 and 6 PCT, in other words the combination of peptides 84, 89 and 1426, optionally in combination with peptides 83 and 87 (claims 1-3, 5, 11-14, 16-26 and 31-33).

NOVELTY (Article 33(2) PCT)

4.1) D1 (example 9) suggests to combine major histocompatibility complex class I and class II binding epitopes in an HCV vaccine. More specifically it is indicated that the epitopes listed in tables XXVI and XXXII may be combined.
Table XXVI depicts A0201-binding peptides, amongst which the epitope YLLPRRGPRL (contained in peptide 83), DLMGYIPLV (an equivalent of peptide 87) and HMWNFISGI (contained in peptide 1426).
Table XXXII mentions HCV epitopes comprising a DR-supermotif, amongst which GQIVGGVYLLPRRGPR (peptide 83) and DLMGYIPLV (an equivalent of peptide 87), and a DR-binding 'collaborator' epitope GYKVLVLNPSVAAT (peptide 84).
Table XII discloses the peptide CINGVCWTA, an analogue of peptide 89.

Although D1 discloses all the compounds of an HCV vaccine composition comprising peptides 84, 89 and 1426, as well as peptides 83 and 87, there is no hint that combining peptides 84, 89 and 1426, optionally with peptides 83 and 87, results in an composition that is suitable as a vaccine and that induces a T cell response both in HLA-A2 transgenic mice and in healthy human individuals.
Subject-matter restricted to an HCV vaccine composition **consisting of peptides 84, 89 and 1426, optionally in addition of peptides 83 and 87**, therefore seems to be novel (Article 33(2) PCT).

4.2) The applicant is informed that HCV viral particles and recombinant HCV viral proteins **comprising** the (hotspot) epitope combination of peptides 84, 89 and 1426 also fall under

the scope of the claims in their present wording. For instance, D2 (claim 1) relates to an HCV vaccine comprising recombinant portions of at least the HCV core NS3 and NS4 proteins that **comprise** peptides 83, 84, 87, 89 and 1426.
In the present wording, claims 1-3, 5, 11-14, 16-26 and 31-33 therefore lack novelty (Article 33(2) PCT).

INVENTIVE STEP (Article 33(3) PCT)

5.1) As indicated above, there is no teaching in the prior art that suggests to select peptides 84, 89 and 1426 for an HCV vaccine combination. An inventive step may be acknowledged for the subject-matter of claims 1-3, 5, 11-14, 16-26 and 31-33, provided that the novelty objection raised under 4.2 is overcome by restriction of the claims to a combination **consisting** of the said three defined epitopes, with optional addition of peptides 83 and 87.

Re Item VIII

Certain observations on the international application

6.1) Claims 27 and 28 seem to refer back to claim 26 instead of claim 25.

6.2) Claim 30 refers to the vaccine of claim 29 comprising twelve HCV epitopes, whereas the vaccine of claim 29 seems to relate to only seven HCV epitopes.

6.3) Claim 23 refers to a vaccine 'in a form which is reconstitutable within 15 minutes at 37 °C. Said claims lacks technical features and does not define the subject-matter for which protection is sought in a manner sufficiently clear for the skilled person.

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